

# Molecular Interactions of Diphenhydramine-hydrochloride with Some Imidazolium-Based Ionic Liquids in Aqueous Media at $T = 293.15\text{--}313.15\text{ K}$ : Volumetric, Acoustic, and UV Absorption Studies

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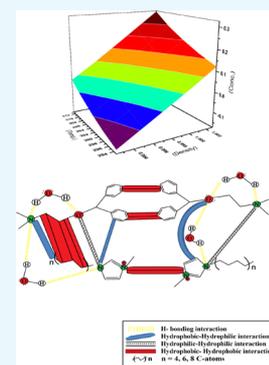
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**ABSTRACT:** From the density ( $\rho$ ) and speed-of-sound ( $u$ ) measurements, the interactions of the drug diphenhydramine-hydrochloride (DPH) with three imidazolium-based ionic liquids (ILs) (1-butyl-3-methylimidazolium chloride,  $[\text{C}_4\text{mim}][\text{Cl}]$ , 1-hexyl-3-methylimidazolium chloride,  $[\text{C}_6\text{mim}][\text{Cl}]$ , and 1-methyl-3-octylimidazolium chloride,  $[\text{C}_8\text{mim}][\text{Cl}]$ ) have been investigated in aqueous medium at  $T = 293.15\text{--}313.15\text{ K}$  and experimental pressure  $p = 0.1\text{ MPa}$ . From the density calculations, the apparent molar volume ( $V_\phi$ ) and the apparent partial molar volumes of transfer ( $\Delta_i V_\phi^o$ ) have been determined for various solutions of DPH in aqueous solutions of different ILs. In addition, from the speed-of-sound data, the apparent molar isentropic compressibility ( $K_\phi$ ), apparent partial molar isentropic compressibility ( $K_\phi^o$ ), and apparent partial molar isentropic compressibility of transfer ( $\Delta_i K_\phi^o$ ) have been calculated. The pair and triplet interaction coefficients are derived from apparent partial molar volumes of transfer. For the present mixtures, the absorption spectra have been also recorded using a UV–visible spectrophotometer. Using Hepler’s constant, the structure-making nature of the solute has been confirmed. All these calculated parameters provide detailed insights into various physicochemical interactions prevailing in the ternary system and confirm the presence of a strong attractive interaction between DPH and ILs.



## 1. INTRODUCTION

Ionic liquids have emerged as powerful and promising green solvents in various industrial and academic areas.<sup>1</sup> In general, ionic liquids are a class of organic salts composed of bulky asymmetric organic cations (e.g., imidazolium, pyridine, etc.) and organic or inorganic anions (e.g., halides) that are liquids below 373 K.<sup>2</sup> The attractiveness of these comforting solvents has been attributed to their unusually unique properties such as very small vapor pressure, a wide liquid range, high thermal stability, and excellent solvent power for organic and inorganic compounds.<sup>3,4</sup> In particular, the low vapor pressure ascribed to their ionic inherent characteristics along with their good thermal stability make them “green” alternatives to conventional hazardous organic solvents.<sup>5</sup> Due to their structural modification activities, ILs are termed as “designer” or “task-specific” solvents. Studies have shown that ionic liquids have efficient applications in the fields of biomass conversion,<sup>6,7</sup> biotransformation,<sup>8</sup> electrochemistry,<sup>9</sup> liquid crystal development,<sup>10</sup> chemical synthesis and catalysis,<sup>11,12</sup> biotechnology, and many other fields like medicine and the pharmaceutical industry.<sup>13,14</sup> Comprehensive studies of ILs can serve to better understand the functional mechanisms of important biomolecules such as amino acids, histidine, etc., which contain imidazole side chains and play a vital role in the structure and binding functions of hemoglobin.

The emerging progress in biotechnology and genetics in the recent times has widened the scientific interest in exploring the action of drugs in biological media.<sup>14</sup> The drug–water molecular

interactions and their temperature dependence play a pivotal role in understanding the drug action.<sup>15</sup> Investigation of thermodynamic, volumetric, and acoustical properties is an important tool in determining the intermolecular interactions occurring in electrolyte solutions. Further, studies on the volumetric and acoustical properties of aqueous ionic liquid–drug solutions provide crucial information on the interactions, solvation, and association behavior of ions in such solutions.<sup>16–20</sup> Abundant studies on the thermodynamics, viscometry, phase equilibria, and surface phenomenon of ILs in pure solution and as mixtures especially with water have been used as the basis for several reactions.<sup>21–24</sup>

In the present work, we have studied the volumetric and acoustic properties of DPH in aqueous mixtures of  $[\text{C}_4\text{mim}][\text{Cl}]$ ,  $[\text{C}_6\text{mim}][\text{Cl}]$ , and  $[\text{C}_8\text{mim}][\text{Cl}]$ . The focus of our work is to present some new thermodynamic properties of the mentioned ternary systems. In the current study, DPH has been chosen as a drug candidate because of its water-soluble nature and its significant medical applications. In medicine, this drug is used to treat insomnia, symptoms of common cold, tremor in Parkinsonism, extrapyramidal symptoms, and

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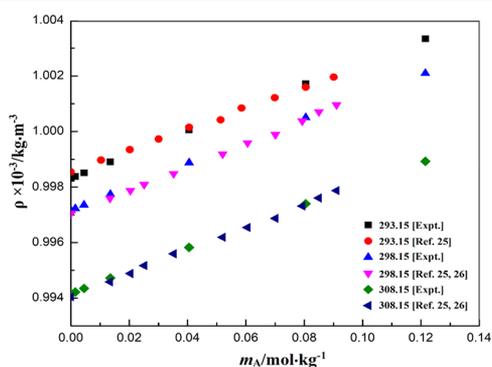


nausea.<sup>25</sup> Further, DPH has a local anesthetic effect that is useful for patients who are susceptible to lidocaine.<sup>26</sup> In an attempt to explore the possible dynamic interaction of DPH with aqueous solutions of ILs, we have recorded the densities and speeds of sound for the solutions of DPH in aqueous solutions of [C<sub>4</sub>mim][Cl], [C<sub>6</sub>mim][Cl], and [C<sub>8</sub>mim][Cl], respectively. To the best of our knowledge, no studies on the densities and speeds of sound for solutions of DPH with aqueous solutions of these ILs have been reported so far. Hence, the present study is aimed to determine the characteristic molecular interactions of DPH with ionic liquids/water systems using a volumetric and acoustic approach. In addition, UV–visible absorption spectra have been recorded to further confirm these molecular interactions. Many researchers have studied the solute–solvent interaction of DPH with aqueous and mixed aqueous solutions by determining the different physicochemical parameters.<sup>25–27</sup> Behdoudi et al. studied the effect of choline-based ionic liquids on the thermodynamics and transport properties of aqueous diphenhydramine-hydrochloride solution.<sup>28</sup> Majdan-Cegincara et al. studied the correlation of water activity in aqueous solutions containing diphenhydramine-hydrochloride drug, (D+)-galactose, (D-)-fructose, (D+)-lactose, and sucrose at 298.15 K.<sup>29</sup>

## 2. RESULTS AND DISCUSSION

**2.1. Volumetric and Compressibility Properties.** The densities of DPH in aqueous solutions of [C<sub>4</sub>mim][Cl], [C<sub>6</sub>mim][Cl], and [C<sub>8</sub>mim][Cl], respectively, have been measured to investigate the existence of intermolecular interactions such as solute–solvent and solute–solvent interactions in the various mixtures at different temperatures.

The experimental values of densities of aqueous DPH solution are compared with literature values<sup>25,26</sup> at  $T = 293.15, 298.15$  and  $308.15$  K as shown in Figure 1, which clearly suggests that the experimental and reported values are in good agreement with each other.



**Figure 1.** Comparison of experimental and literature values<sup>25,26</sup> of the densities of DPH + water mixture at three different temperatures.

**2.1.1. Apparent Molar Volume.** The experimental values of densities ( $\rho$ ) of the binary system, i.e., DPH in water, and ternary system, i.e., DPH in (0.005, 0.010, 0.020, and 0.040) mol·kg<sup>-1</sup> aqueous solutions of [C<sub>4</sub>mim][Cl], [C<sub>6</sub>mim][Cl], and [C<sub>8</sub>mim][Cl] respectively, recorded in the temperature range  $T = 293.15$ – $313.15$  K are given in Table 1. It can be observed from Table 1 that the densities of the mixtures (DPH + water + ILs) decrease with the increase in temperature. However, the densities of solutions show an increasing trend with the increasing concentration of ionic liquids.

The apparent molar volumes ( $V_\phi$ ) of DPH in the solutions under investigation are evaluated according to eq 1

$$V_\phi = (M/\rho) - [(\rho - \rho^o)/m_A \rho \rho^o] \quad (1)$$

where  $M$  and  $m_A$  represent the molar mass and molality of DPH in aqueous IL solution, and  $\rho$  and  $\rho^o$  are the densities of the solutions containing DPH + ILs + water and DPH + water mixtures, respectively. The  $V_\phi$  values of DPH as a function of its molality ( $m_A$ ) at the experimental temperatures are given in Table 1. Figures 2–4 denote the plot of the apparent molar volume ( $V_\phi$ ) versus molality ( $m_A$ ) of DPH in aqueous solutions of [C<sub>4</sub>mim][Cl], [C<sub>6</sub>mim][Cl], and [C<sub>8</sub>mim][Cl], respectively. From these plots, we can interpret that  $V_\phi$  values increase with increasing IL concentration at all temperatures. However, the increase is more in case of [C<sub>8</sub>mim][Cl] as compared to [C<sub>6</sub>mim][Cl] and [C<sub>4</sub>mim][Cl]. The limiting value of the apparent molar volume ( $V_\phi^o$ ) at infinite dilution is represented by  $V_\phi^o$  and is calculated using Masson's equation<sup>19,30</sup> given below:

$$V_\phi = V_\phi^o + S_V^* m_A \quad (2)$$

where  $S_V^*$  is the semiempirical solute–solvent interaction coefficient and  $m_A$  is the molality of DPH in an aqueous IL solution. The values of  $V_\phi^o$  and  $S_V^*$  accompanied by their standard error are derived by linear fitting of  $V_\phi$  and are reported in Table S2 of the Supporting Information. As the solute–solvent interactions are negligible at infinite dilution, we can obtain important information pertaining to the solute–solvent interactions from the  $V_\phi^o$  values.<sup>31,32</sup> The  $V_\phi^o$  values of DPH in aqueous [C<sub>4</sub>mim][Cl], [C<sub>6</sub>mim][Cl], and [C<sub>8</sub>mim][Cl] solutions reflect the presence of solute–solvent interactions.<sup>19,33</sup> The  $V_\phi^o$  values increase with increase in the ionic liquid molality ( $m_B$ ), which indicates the strengthening of attractive interactions between DPH and the studied ionic liquids.<sup>33,38</sup>

In the current study,  $V_\phi^o$  increases as the chain length of ILs increases. It therefore shows that ILs with high molar mass have higher  $V_\phi^o$  value than those with lower molar mass. In other words,  $V_\phi^o$  values are higher for [C<sub>8</sub>mim][Cl] as compared to [C<sub>6</sub>mim][Cl] and [C<sub>4</sub>mim][Cl]. This can be interpreted based on the hydration behavior of ionic liquids. ILs with shorter chain length have greater affinity for water.<sup>34,35</sup> The reason for this behavior is the increase in the hydrophobicity of ionic liquids with increasing chain length from butyl to hexyl to octyl, which reduces their interactions with water molecules. Therefore, [C<sub>4</sub>mim][Cl]–water interactions are stronger compared to [C<sub>6</sub>mim][Cl]–water interactions, which in turn are stronger compared to [C<sub>8</sub>mim][Cl]–water interactions. Among these ILs, [C<sub>8</sub>mim][Cl], due to its weaker interaction with water, is expected to have a stronger interaction with DPH, as shown by the higher  $V_\phi^o$  values obtained for DPH in the aqueous [C<sub>8</sub>mim][Cl] solution.<sup>30,36,37</sup> From Table S2, it can be seen that the magnitude of  $S_V^*$  is positive for all concentrations of DPH at all temperature conditions. The positive values of  $S_V^*$  are indicative of the presence of solute–solvent interactions. Since a regular trend is not observed for  $S_V^*$  values, it follows that other factors also affect the solute–solvent interactions.<sup>38</sup> The dominance of solute–solvent interaction over solute–solvent interaction is due to the higher  $V_\phi^o$  values.<sup>19,33</sup> The increase in solvation of the drug at higher temperatures as well as at higher concentrations of ionic liquid that involves release of some solvent molecules from the loose solvation layers of the solute into the solution may be the reason for the increase in values of  $V_\phi^o$  for DPH in aqueous solutions of ILs. Similarly, due to the

**Table 1. Densities ( $\rho$ ) and Apparent Molar Volumes ( $V_\phi$ ) of DPH in Aqueous Solutions of  $[C_4\text{mim}][\text{Cl}]$ ,  $[C_6\text{mim}][\text{Cl}]$ , and  $[C_8\text{mim}][\text{Cl}]$  at Five Different Temperatures and Atmospheric Pressure  $p = 0.1$  MPa**

$a_{m_A}$ (mol·kg <sup>-1</sup> )	$\rho \times 10^{-3}$ (kg·m <sup>-3</sup> )					$V_\phi \times 10^6$ (m <sup>3</sup> ·mol <sup>-1</sup> )				
	temp.					temp.				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	293.15K	298.15 K	303.15 K	308.15 K	313.15 K
	H <sub>2</sub> O + DPH									
0.0000	0.998313	0.997160	0.995769	0.994155	0.994155					
0.0015	0.998379	0.997225	0.995833	0.994218	0.994218	248.08	248.98	249.95	250.96	252.01
0.0045	0.998511	0.997355	0.995961	0.994344	0.994344	248.12	249.02	249.98	250.99	252.05
0.0135	0.998904	0.997742	0.996342	0.994719	0.994719	248.24	249.15	250.11	251.12	252.18
0.0405	1.000061	0.998879	0.997464	0.995822	0.995822	248.57	249.53	250.42	251.47	252.50
0.0805	1.001715	1.000506	0.999074	0.997395	0.997395	249.06	250.01	250.82	251.99	253.08
0.1215	1.003342	1.002097	1.000642	0.998925	0.998925	249.52	250.54	251.38	252.60	253.73
	0.005 mol·kg <sup>-1</sup> $[C_4\text{mim}][\text{Cl}]$ + DPH									
0.0000	0.998279	0.997116	0.995721	0.994107	0.992280					
0.0015	0.998340	0.997178	0.995782	0.994167	0.992339	250.10	251.02	251.99	252.99	254.06
0.0045	0.998466	0.997302	0.995904	0.994287	0.992457	250.13	251.04	252.01	253.02	254.09
0.0135	0.998842	0.997672	0.996268	0.994645	0.992809	250.18	251.10	252.06	253.08	254.15
0.0405	0.999952	0.998764	0.997343	0.995701	0.993849	250.40	251.32	252.27	253.32	254.34
0.0805	1.001551	1.000334	0.998890	0.997222	0.995344	250.69	251.64	252.56	253.56	254.65
0.1215	1.003125	1.001884	1.000422	0.998729	0.996821	251.06	251.99	252.85	253.88	254.96
	0.010 mol·kg <sup>-1</sup> $[C_4\text{mim}][\text{Cl}]$ + DPH									
0.0000	0.998336	0.997173	0.995774	0.994163	0.992143					
0.0015	0.998397	0.997233	0.995835	0.994222	0.9923 97	251.42	252.34	253.31	254.33	255.40
0.0045	0.998519	0.997353	0.995953	0.994338	0.992511	251.46	252.37	253.34	254.37	255.44
0.0135	0.998883	0.997711	0.996305	0.994684	0.992851	251.51	252.43	253.40	254.43	255.50
0.0405	0.999958	0.998768	0.997344	0.995706	0.993852	251.71	252.63	253.61	254.62	255.77
0.0805	1.001506	1.000289	0.998835	0.997171	0.995291	251.99	252.93	253.95	254.97	256.08
0.1215	1.003035	1.001788	1.000305	0.998616	0.996707	252.31	253.27	254.31	255.32	256.44
	0.020 mol·kg <sup>-1</sup> $[C_4\text{mim}][\text{Cl}]$ + DPH									
0.0000	0.998439	0.997274	0.995872	0.994255	0.992416					
0.0015	0.998498	0.997332	0.995929	0.994313	0.992469	252.75	253.67	254.67	255.66	256.74
0.0045	0.998616	0.997448	0.996043	0.994425	0.992579	252.77	253.69	254.67	255.70	256.78
0.0135	0.998968	0.997794	0.996383	0.994759	0.992907	252.83	253.76	254.73	255.76	256.84
0.0405	1.000006	0.998814	0.997385	0.995743	0.993874	253.07	253.99	254.97	256.01	257.07
0.0805	1.001501	1.000281	0.998821	0.997154	0.995263	253.34	254.29	255.34	256.35	257.38
0.1215	1.002971	1.001724	1.000234	0.998543	0.996627	253.70	254.66	255.71	256.71	257.75
	0.040 mol·kg <sup>-1</sup> $[C_4\text{mim}][\text{Cl}]$ + DPH									
0.0000	0.998747	0.997567	0.996156	0.994521	0.992487					
0.0015	0.998804	0.997623	0.996213	0.994577	0.992539	254.02	254.95	255.91	256.95	258.02
0.0045	0.998918	0.997735	0.996323	0.994685	0.992645	254.05	254.97	255.95	256.99	258.05
0.0135	0.999258	0.998069	0.996651	0.995007	0.992961	254.11	255.04	256.02	257.05	258.11
0.0405	1.000260	0.999053	0.997617	0.995955	0.993891	254.35	255.28	256.27	257.31	258.35
0.0805	1.001698	1.000463	0.999007	0.997313	0.995226	254.68	255.64	256.55	257.67	258.68
0.1215	1.003110	1.001849	1.000371	0.998646	0.996527	255.07	256.02	256.92	258.05	259.07
	0.005 mol·kg <sup>-1</sup> $[C_6\text{mim}][\text{Cl}]$ + DPH									
0.0000	0.998175	0.997176	0.995779	0.994274	0.992348					
0.0015	0.998412	0.997233	0.995837	0.994331	0.992701	252.09	253.01	253.98	254.98	256.01
0.0045	0.998532	0.997351	0.995953	0.994445	0.992813	252.12	253.05	254.02	255.02	256.05
0.0135	0.998889	0.997702	0.996298	0.994784	0.993146	252.26	253.18	254.15	255.16	256.19
0.0405	0.999941	0.998737	0.997313	0.995782	0.994126	252.54	253.44	254.47	255.45	256.49
0.0805	1.001452	1.000225	0.998767	0.997215	0.995534	252.88	253.75	254.86	255.79	256.81
0.1215	1.002941	1.001682	1.000197	0.998625	0.996924	253.24	254.18	255.25	256.15	257.13
	0.010 mol·kg <sup>-1</sup> $[C_6\text{mim}][\text{Cl}]$ + DPH									
0.0000	0.998352	0.997174	0.995779	0.994274	0.992645					
0.0015	0.998448	0.997323	0.995943	0.994408	0.992391	253.41	254.33	255.30	256.31	257.43
0.0045	0.998564	0.997437	0.996055	0.994518	0.992499	253.45	254.37	255.34	256.35	257.47
0.0135	0.998909	0.997776	0.996388	0.994845	0.992820	253.59	254.50	255.48	256.49	257.62
0.0405	0.999927	0.998775	0.997368	0.995807	0.993765	253.83	254.77	255.77	256.79	257.90
0.0805	1.001391	1.000208	0.998774	0.997186	0.995119	254.13	255.12	256.12	257.15	258.25
0.1215	1.002828	1.001608	1.000144	0.998528	0.996442	254.51	255.57	256.60	257.64	258.69
	0.020 mol·kg <sup>-1</sup> $[C_6\text{mim}][\text{Cl}]$ + DPH									

Table 1. continued

$^a m_A$ (mol·kg <sup>-1</sup> )	$\rho \times 10^{-3}$ (kg·m <sup>-3</sup> )					$V_\phi \times 10^6$ (m <sup>3</sup> ·mol <sup>-1</sup> )				
	temp.					temp.				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	293.15K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	0.998481	0.997358	0.995991	0.994205	0.992483					
0.0015	0.998537	0.997413	0.996045	0.994468	0.992718	254.74	255.65	256.62	257.64	258.71
0.0045	0.998649	0.997523	0.996153	0.994574	0.992822	254.77	255.69	256.66	257.69	258.75
0.0135	0.998982	0.99785	0.996474	0.994889	0.993131	254.91	255.83	256.80	257.83	258.89
0.0405	0.999962	0.998813	0.997418	0.995816	0.99404	255.21	256.10	257.11	258.11	259.19
0.0805	1.001368	1.000192	0.998768	0.997142	0.995341	255.55	256.47	257.50	258.49	259.55
0.1215	1.002748	1.001544	1.000085	0.998435	0.996609	255.94	256.88	257.97	258.95	260.01
	0.040 mol·kg <sup>-1</sup> [C <sub>6</sub> mim][Cl] + DPH									
0.0000	0.998829	0.997486	0.996062	0.994428	0.992872					
0.0015	0.998883	0.997740	0.996353	0.994781	0.992920	255.99	256.92	257.89	258.92	260.02
0.0045	0.998991	0.997846	0.996457	0.994883	0.993020	256.04	256.96	257.94	258.96	260.06
0.0135	0.999312	0.998161	0.996766	0.995186	0.993317	256.18	257.10	258.08	259.11	260.21
0.0405	1.000255	0.999087	0.997674	0.996077	0.994191	256.50	257.41	258.39	259.40	260.48
0.0805	1.001604	1.000412	0.998973	0.997353	0.995444	256.89	257.78	258.77	259.75	260.80
0.1215	1.002921	1.001702	1.000239	0.998595	0.996667	257.35	258.26	259.22	260.21	261.22
	0.005 mol·kg <sup>-1</sup> [C <sub>8</sub> mim][Cl] + DPH									
0.0000	0.998410	0.997242	0.995833	0.994426	0.993014					
0.0015	0.998467	0.997298	0.995888	0.994480	0.993067	254.08	255.01	255.98	256.97	257.96
0.0045	0.998581	0.997410	0.995998	0.994588	0.993173	254.12	255.04	256.02	257.01	257.99
0.0135	0.998920	0.997743	0.996325	0.994909	0.993488	254.26	255.18	256.16	257.15	258.14
0.0405	0.999916	0.998723	0.997285	0.995852	0.994414	254.59	255.48	256.51	257.48	258.45
0.0805	1.001341	1.000125	0.998652	0.997198	0.995736	255.01	255.87	257.00	257.91	258.87
0.1215	1.002739	1.001496	0.999984	0.998517	0.997027	255.43	256.33	257.52	258.34	259.33
	0.010 mol·kg <sup>-1</sup> [C <sub>8</sub> mim][Cl] + DPH									
0.0000	0.998410	0.997242	0.995833	0.994426	0.993014					
0.0015	0.998440	0.997375	0.996007	0.994541	0.992721	255.41	256.32	257.29	258.29	259.38
0.0045	0.998495	0.997427	0.996060	0.994593	0.992772	255.45	256.36	257.33	258.33	259.42
0.0135	0.998605	0.997535	0.996166	0.994697	0.992874	255.59	256.50	257.47	258.48	259.57
0.0405	0.998932	0.997856	0.996481	0.995006	0.993177	255.79	256.85	257.80	258.79	259.85
0.0805	0.999898	0.998798	0.997406	0.995914	0.994068	256.21	257.24	258.22	259.22	260.24
0.1215	1.001276	1.000146	0.998727	0.997209	0.995341	256.66	257.73	258.68	259.66	260.74
	0.020 mol·kg <sup>-1</sup> [C <sub>8</sub> mim][Cl] + DPH									
0.0000	0.998514	0.997442	0.995127	0.994593	0.992912					
0.0015	0.998567	0.997494	0.996178	0.994643	0.992961	256.74	257.64	258.61	259.63	260.69
0.0045	0.998673	0.997598	0.99628	0.994743	0.993059	256.77	257.68	258.65	259.67	260.73
0.0135	0.998988	0.997907	0.996583	0.995040	0.993350	256.92	257.83	258.80	259.82	260.88
0.0405	0.999914	0.998815	0.997473	0.995912	0.994205	257.22	258.14	259.11	260.14	261.18
0.0805	1.001238	1.000114	0.998744	0.997159	0.995426	257.61	258.51	259.51	260.51	261.56
0.1215	1.002532	1.001385	0.999988	0.998376	0.996615	258.05	258.93	259.92	260.94	262.01
	0.040 mol·kg <sup>-1</sup> [C <sub>8</sub> mim][Cl] + DPH									
0.0000	0.9989	0.997799	0.996456	0.994919	0.992467					
0.0015	0.998951	0.997849	0.996507	0.994967	0.993309	257.99	258.90	259.88	260.90	261.96
0.0045	0.999053	0.997949	0.996605	0.995063	0.993403	258.03	258.94	259.92	260.94	262.01
0.0135	0.999356	0.998246	0.996896	0.995348	0.993682	258.17	259.09	260.07	261.09	262.15
0.0405	1.000246	0.999119	0.99775	0.996185	0.994501	258.49	259.38	260.39	261.39	262.46
0.0805	1.001521	1.000369	0.998972	0.997384	0.995673	258.83	259.73	260.75	261.73	262.80
0.1215	1.002764	1.001589	1.000166	0.998551	0.996811	259.27	260.14	261.15	262.15	263.25

$^a m_A$  represents the molality of DPH in aqueous IL solution. Standard uncertainties are  $u(p) = 0.01$  MPa,  $u(T) = 0.01$  K,  $u(\rho) = 0.32$  kg m<sup>-3</sup>,  $u(m_A) = 2 \times 10^{-3}$  mol·kg<sup>-1</sup>, and  $u(V_\phi) = (0.03-0.05) \times 10^6$  m<sup>3</sup>·mol<sup>-1</sup>.

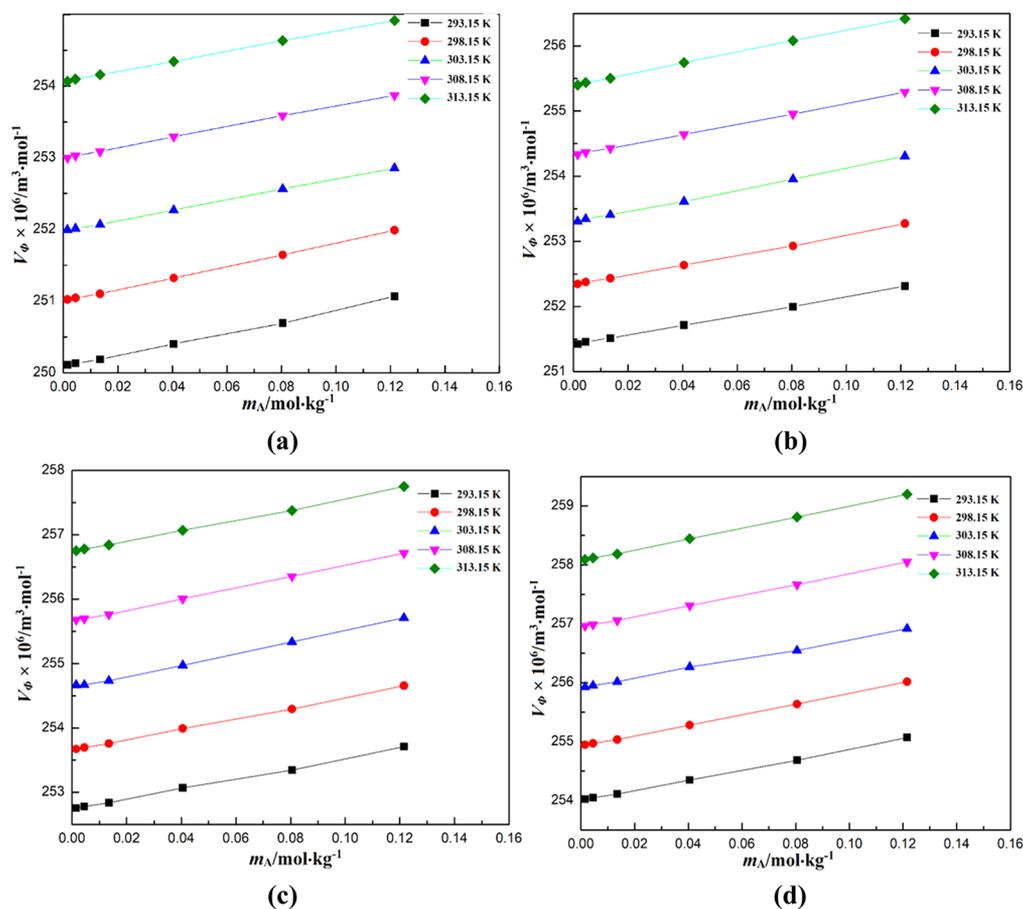
strong attractive interactions owing to hydration of ions, the  $V_\phi^o$  values increase with the increase in drug concentration. Limiting apparent molal volumes are recognized to be sensitive to solute solvation, which provides insight regarding the structural volume of the solute in solvent and the volume change of the solvent in the event of shell formation around the ion.<sup>39-41</sup>

The transfer volumes ( $\Delta_t V_\phi^o$ ) for DPH in water and DPH in aqueous [C<sub>4</sub>mim][Cl], [C<sub>6</sub>mim][Cl], and [C<sub>8</sub>mim][Cl]

solutions have been computed using eq 3 and their values are reported in Table S3.

$$\Delta_t V_\phi^o = V_\phi^o \text{ (in aqueous ionic liquids)} - V_\phi^o \text{ (in water)} \quad (3)$$

The literature values of  $V_\phi^o$  of DPH in water are compared with the experimental values and found to be in good agreement. From Table S3, it follows that the values of  $\Delta_t V_\phi^o$  are positive



**Figure 2.** Plots of apparent molar volume ( $V_\phi$ ) versus molality ( $m_A$ ) of (a) DPH in  $0.005 \text{ mol}\cdot\text{kg}^{-1}$ , (b) DPH in  $0.010 \text{ mol}\cdot\text{kg}^{-1}$ , (c) DPH in  $0.020 \text{ mol}\cdot\text{kg}^{-1}$ , and (d) DPH in  $0.040 \text{ mol}\cdot\text{kg}^{-1}$  aqueous  $[\text{C}_4\text{mim}][\text{Cl}]$  solution at different temperatures.

and increase with increasing ionic liquid molality. According to the co-sphere overlap model of ternary mixtures,<sup>42–44</sup> some kinds of interactions between the solute (DPH) and cosolute molecules (ILs are cosolute) in water are possible: (1) hydrophilic–ionic, (2) hydrophilic–hydrophilic, (3) hydrophilic–hydrophobic, and (4) hydrophobic–hydrophobic interactions arising due to different groups of DPH and ionic liquids. Taking this model as the guideline, the hydrophilic–ionic and hydrophilic–hydrophilic interactions would lead to positive values of  $\Delta_t V_\phi^\circ$ , and hydrophilic–hydrophobic and hydrophobic–hydrophobic interactions would lead to negative  $\Delta_t V_\phi^\circ$  values. In the current case, the observed positive values of  $\Delta_t V_\phi^\circ$  have been credited to ionic–hydrophilic interactions, which are stronger than ionic–hydrophobic and hydrophobic–hydrophobic interactions and arise due to the polar groups of DPH molecules and the ionic and polar groups of ILs.<sup>19</sup> In addition, their values increase at high IL concentration, indicating the strengthening of these types of interactions in the studied range of concentration.

The model by Shahidi and co-workers<sup>45</sup> also shows that positive  $\Delta_t V_\phi^\circ$  values lead to decrease in the contraction volume. The values of  $\Delta_t V_\phi^\circ$  in the investigated solutions show the following trend:  $[\text{C}_4\text{mim}][\text{Cl}] > [\text{C}_6\text{mim}][\text{Cl}] > [\text{C}_8\text{mim}][\text{Cl}]$ , which indicates that strong solute–solvent interactions are prevailing in the ternary system.<sup>46,47</sup>

### 2.1.2. Pair and Triplet Volumetric Interaction Coefficients.

The transfer volumes ( $\Delta_t V_\phi^\circ$ ) of the solution may also be specified by the McMillan Mayer theory of solutions,<sup>48</sup> which

separates the transfer volumes effect into two different parts, i.e., interaction between solute–solute molecules and interaction between more than two solute molecules. This theory is further discussed in detail by Friedmann and Krishnan,<sup>49</sup> which states that solute–cosolute interactions can be included in the solvation spheres. So, transfer volumes ( $\Delta_t V_\phi^\circ$ ) can be expressed in terms of pair and triplet coefficients and are represented by eq 4

$$\Delta_t V_\phi^\circ = 2V_{AB} \cdot m_B + 3V_{ABB} \cdot m_B^2 \quad (4)$$

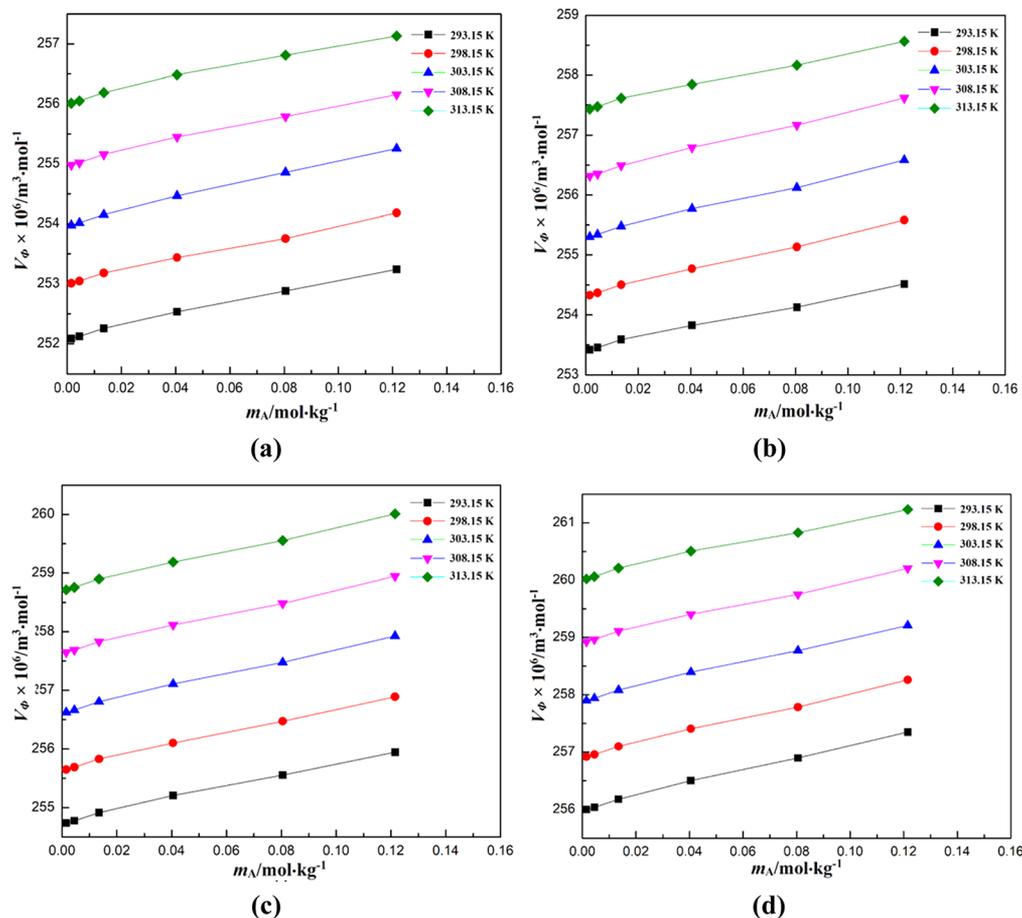
where  $A$  stands for DPH,  $B$  stands for the ILs, and  $V_{AB}$  and  $V_{ABB}$  are the paired and triplet volumetric interaction parameter, respectively.

These parameters were obtained by fitting the above equation to the  $\Delta_t V_\phi^\circ$  data shown in Table 2. The  $V_{AB}$  and  $V_{ABB}$  values of all investigated solutions are positive and negative, respectively. The magnitudes of both interaction coefficients decrease with the increasing temperature. In addition, the magnitude of  $V_{AB}$  is greater than that of  $V_{ABB}$ , which suggests that the interactions between DPH and the ILs are mainly pairwise.

**2.1.3. Temperature-Dependent Partial Molar Volumes.** In the present studied solutions, the temperature-dependent standard partial molar volume is positive for DPH and can be expressed by the following equation:

$$V_\phi^\circ = A + B(T - T_{\text{ref}}) + C(T - T_{\text{ref}})^2 \quad (5)$$

Here,  $A$ ,  $B$ , and  $C$  represent empirical parameters,  $T$  is the temperature in Kelvin, and  $T_{\text{ref}} = 303.15 \text{ K}$ . The values of  $A$ ,  $B$ ,



**Figure 3.** Plots of apparent molar volume ( $V_\phi$ ) versus molality ( $m_A$ ) of (a) DPH in  $0.005 \text{ mol}\cdot\text{kg}^{-1}$ , (b) DPH in  $0.010 \text{ mol}\cdot\text{kg}^{-1}$ , (c) DPH in  $0.020 \text{ mol}\cdot\text{kg}^{-1}$ , and (d) DPH in  $0.040 \text{ mol}\cdot\text{kg}^{-1}$  aqueous  $[\text{C}_6\text{mim}][\text{Cl}]$  solution at different temperatures.

and  $C$  could be obtained by using polynomial fits of the  $V_\phi^\circ$  values in the experimental temperature range. The theoretical values of  $V_\phi^\circ$  were calculated using these parameters and the average relative deviations (ARDs) obtained from experimental and theoretical values are also reported in Table S4.

The average relative deviations (ARDs) were calculated using the following eq 6

$$\text{ARD} = (1/n) \sum [(X_{\text{exp}} - X_{\text{cal}})/X_{\text{exp}}] \quad (6)$$

where  $X$  is equal to  $V_\phi^\circ$ , the apparent molar volume at infinite dilution. The values summarized in Table S4 for ARD are found to be quite small, indicating that the polynomial equation fits very well in the present study.

The limiting apparent molar expansibility is calculated using eq 7

$$E_\phi^\circ = (\partial V_\phi^\circ / \partial T)_P = B + 2C(T - T_{\text{ref}}) \quad (7)$$

The  $E_\phi^\circ$  arises from two major components in the case of the electrolyte, i.e.,  $E_\phi^\circ$  (Str.) and  $E_\phi^\circ$  (Elec.), as specified below:

$$E_\phi^\circ = E_\phi^\circ(\text{Str.}) + E_\phi^\circ(\text{Elec.}) \quad (8)$$

where  $E_\phi^\circ$  (Str.) signifies the standard apparent molar expansibility, which is accountable for the alteration in the structure of the solvent, while  $E_\phi^\circ$  (Elec.) is the standard apparent molar expansibility due to electrostriction changes, i.e., the contribution of the hydration layer around the solutes. The structural component is predominant at lower temperatures, i.e.,

$E_\phi^\circ$  (Str.)  $>$   $E_\phi^\circ$  (Elec.), whereas the electrostriction component is predominant at higher temperatures, i.e.,  $E_\phi^\circ$  (Elec.)  $>$   $E_\phi^\circ$  (Str.). The calculated values of  $E_\phi^\circ$  for DPH in the investigated aqueous IL solutions are given in Table 3.

The  $E_\phi^\circ$  values give insight regarding solute–solvent interactions.<sup>50</sup> The  $E_\phi^\circ$  values are found to be positive for the studied solute, which is indicative of the fact that a number of solvent molecules might be unconfined from the layers of solvation upon heating. The positive expansibility is a property of aqueous hydrophobic hydration solutions. This causes the solution volume to increase a little more quickly than that of pure water, and so  $E_\phi^\circ$  would present positive values.<sup>51</sup> These observations signify the existence of competitive hydrophilic and hydrophobic interactions in the mixture. The sign of the temperature derivative of the partial molar expansibility, i.e.,  $(\partial E_\phi^\circ / \partial T)_P$ , is a useful parameter in exemplifying the structure-making and breaking ability of a solute in the solution, which is known as Hepler's constant.

A negative sign of  $(\partial E_\phi^\circ / \partial T)_P$  signifies the solute as a structure breaker and a positive sign confirms it as a structure maker.<sup>48,50</sup> The general thermodynamic expression described by Hepler is given below:

$$(\partial E_\phi^\circ / \partial T)_P = (\partial^2 V_\phi^\circ / \partial T^2)_P = 2C \quad (9)$$

The values of the temperature derivative of partial molar expansibility  $(\partial E_\phi^\circ / \partial T)_P$  are tabulated in Table 3. The  $(\partial E_\phi^\circ / \partial T)_P$  values of DPH in the aqueous ILs are very small and positive, and increase with increase in the concentration of ionic



**Table 3. Limiting Apparent Molar Expansibility ( $E_{\phi}^{\circ}$ ) of DPH in Aqueous Solutions of  $[C_4mim][Cl]$ ,  $[C_6mim][Cl]$ , and  $[C_8mim][Cl]$  at Five Different Temperatures**

${}^a m_B$ (mol·kg <sup>-1</sup> )	$E_{\phi}^{\circ}$ (m <sup>3</sup> ·mol <sup>-1</sup> ·K <sup>-1</sup> )					$(\partial E_{\phi}^{\circ}/\partial T)_P \times 10^6$ (m <sup>3</sup> ·mol <sup>-1</sup> ·K <sup>-2</sup> )
	$T = 293.15$ K	$T = 298.15$ K	$T = 303.15$ K	$T = 308.15$ K	$T = 313.15$ K	
	[C <sub>4</sub> mim][Cl]					
0.000	0.176	0.185	0.195	0.204	0.212	0.00182
0.005	0.178	0.188	0.198	0.208	0.218	0.00196
0.010	0.177	0.189	0.199	0.210	0.220	0.00216
0.020	0.178	0.190	0.200	0.211	0.221	0.00214
0.040	0.179	0.192	0.204	0.216	0.229	0.00252
	[C <sub>6</sub> mim][Cl]					
0.000	0.176	0.185	0.195	0.204	0.212	0.00182
0.005	0.181	0.189	0.198	0.206	0.214	0.00162
0.010	0.172	0.186	0.200	0.214	0.228	0.00272
0.020	0.178	0.189	0.199	0.210	0.220	0.00212
0.040	0.179	0.190	0.202	0.214	0.226	0.00236
	[C <sub>8</sub> mim][Cl]					
0.000	0.176	0.185	0.195	0.204	0.212	0.00182
0.005	0.177	0.186	0.195	0.205	0.213	0.00176
0.010	0.178	0.188	0.198	0.208	0.217	0.00200
0.020	0.179	0.189	0.199	0.209	0.218	0.00196
0.040	0.181	0.190	0.200	0.210	0.219	0.00190

<sup>a</sup> $m_B$  represents the molality of the aqueous IL solution.

determine the number of water molecules that hydrate the solute molecules. Two different approaches are used to calculate the hydration number, i.e., from the electrostriction partial molar volume and from the electrostriction partial molar compressibility. However, in the present case, hydration number is calculated from the electrostriction partial molar volume using the following equation:<sup>19,52</sup>

$$n_H = V_{\phi}^{\circ}(\text{Elec.}) / (V_{\phi,E}^{\circ} - V_{\phi,B}^{\circ}) \quad (10)$$

In the above equation,  $V_{\phi,E}^{\circ}$  represents the molar volume of electrostricted water and  $V_{\phi,B}^{\circ}$  represents the molar volume of bulk water. Hydration of DPH is represented by the term  $V_{\phi}^{\circ}(\text{Elec.})$ , called as the electrostriction partial molar volume. The denominator in eq 10 ( $V_{\phi,E}^{\circ} - V_{\phi,B}^{\circ}$ ) has values of  $-3.3$ ,  $-3.7$ , and  $-4.0$  cm<sup>3</sup> mol<sup>-1</sup> at 298.15, 303.15, and 308.15 K, respectively.<sup>19,52</sup> The limiting apparent molar volume of DPH can be represented as

$$V_{\phi}^{\circ}(\text{DPH}) = V_{\phi}^{\circ}(\text{int.}) + V_{\phi}^{\circ}(\text{Elec.}) \quad (11)$$

$V_{\phi}^{\circ}(\text{int.})$  in the above equation represents the intrinsic partial molar volume of DPH and is subsequently calculated using eq 12 as

$$V_{\phi}^{\circ}(\text{int.}) = (0.7/0.634) V_{\phi}^{\circ}(\text{crystal}) \quad (12)$$

The values 0.7 and 0.634 demonstrate the packing density of constituents in an organic crystal and in an arbitrary packing sphere, respectively.  $V_{\phi}^{\circ}(\text{crystal}) = M/\rho_{(\text{crystal})}$ , where  $M$  is the molecular mass and  $\rho_{(\text{crystal})}$  is the crystal density of the solute. The crystal density ( $\rho_{(\text{crystal})}$ ) value of DPH is 1.222 g·cm<sup>-3</sup> and is taken from the literature.<sup>53</sup> The value of hydration number ( $n_H$ ) is calculated considering the volumetric model and is displayed in Table S5 of the Supporting Information. From Table S5, it is suggested that with the rising temperature,  $n_H$  values show a deteriorating trend, which further signifies decreased electrostriction. Notably, a similar trend is followed with the increase in concentration of the ionic liquid, i.e., the  $n_H$  values for DPH in ionic liquid are lesser than those in water. The

observed pattern suggests strong solute–cosolute interactions (between ions of the ionic liquid and the end groups of DPH) with the increasing ionic liquid concentration, which in turn is ascribed to the enhanced electrostriction effect of DPH.

**2.2. Speed-of-Sound Measurements.** The speed-of-sound values of DPH in water and DPH in (0.005, 0.010, 0.020, and 0.040) mol·kg<sup>-1</sup> aqueous solution of  $[C_4mim][Cl]$ ,  $[C_6mim][Cl]$ , and  $[C_8mim][Cl]$  in the temperature range 293.15–313.15 K are listed in Table 4.

Further, the experimental values of the speed of sound for DPH in water have been compared with the literature values<sup>25,26</sup> and have been found to be in good accordance with the literature values, which is clearly seen in Figure 5.

**2.2.1. Apparent Molar Isentropic Compressibility.** The apparent molar isentropic compressibility ( $K_{\phi}$ ) values of DPH in aqueous IL solutions of  $[C_4mim][Cl]$ ,  $[C_6mim][Cl]$ , and  $[C_8mim][Cl]$  at different temperatures were calculated using eq 13

$$K_{\phi} = (Mk_s/\rho) - [(k_s^{\circ}\rho - k_s\rho^{\circ})/(m_A\rho\rho^{\circ})] \quad (13)$$

where the definitions of  $M$ ,  $m_A$ ,  $\rho$ , and  $\rho^{\circ}$  have already been discussed below eq 1.  $k_s$  and  $k_s^{\circ}$  are the isentropic compressibility of solution and pure solvent respectively. Isentropic compressibility is calculated using the following relation:

$$K_s = 1/\rho u^2 \quad (14)$$

where  $u$  represents the speed of sound and  $\rho$  represents the density of the corresponding solutions. The calculated values of  $K_{\phi}$  for DPH in (0.005, 0.01, 0.02, and 0.04) mol·kg<sup>-1</sup> of aqueous IL solutions in the experimental temperature range are given in Table 4. As per the analysis in Table 4,  $K_{\phi}$  values are negative at different temperatures and their magnitude decrease with increasing temperature as well as increasing concentration of ILs.

We can infer that positive  $K_{\phi}$  values in aqueous solution correspond to hydrophobic solutes; negative and large  $K_{\phi}$  values

**Table 4. Speed of Sound ( $u$ ) and Apparent Molar Isentropic Compressibility ( $K_\phi$ ) of DPH in Aqueous Solutions of  $[C_4mim][Cl]$ ,  $[C_6mim][Cl]$ , and  $[C_8mim][Cl]$  at Five Different Temperatures**

$^a m_A$ (mol·kg <sup>-1</sup> )	$u \times 10^3$ (m·s <sup>-1</sup> )					$K_\phi \times 10^{15}$ (m <sup>3</sup> ·mol <sup>-1</sup> ·Pa <sup>-1</sup> )				
	temp.					temp.				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
	water + DPH									
0.0000	1.48327	1.49769	1.51005	1.52050	1.52987					
0.0015	1.48358	1.49800	1.51035	1.52079	1.53015	-34.30	-29.11	-24.33	-19.33	-14.10
0.0045	1.48420	1.49860	1.51094	1.52136	1.53070	-34.25	-29.06	-24.29	-19.28	-14.04
0.0135	1.48606	1.50042	1.51271	1.52308	1.53236	-34.11	-28.90	-24.13	-19.12	-13.91
0.0405	1.49164	1.50587	1.51802	1.52822	1.53732	-33.77	-28.52	-23.72	-18.63	-13.56
0.0805	1.49990	1.51392	1.52586	1.53582	1.54465	-33.23	-27.93	-23.20	-18.09	-12.99
0.1215	1.50835	1.52215	1.53388	1.54358	1.55213	-32.67	-27.30	-22.61	-17.45	-12.33
	0.005 mol·kg <sup>-1</sup> $[C_4mim][Cl]$ + DPH									
0.0000	1.48276	1.49707	1.50963	1.52035	1.52921					
0.0015	1.48307	1.49737	1.50992	1.52063	1.52948	-32.15	-26.64	-20.46	-15.18	-9.62
0.0045	1.48369	1.49797	1.51050	1.52119	1.53002	-32.06	-26.55	-20.39	-15.13	-9.54
0.0135	1.48554	1.49977	1.51223	1.52287	1.53163	-31.88	-26.37	-20.24	-15.01	-9.41
0.0405	1.49107	1.50516	1.51743	1.52789	1.53644	-31.28	-25.83	-19.79	-14.58	-9.00
0.0805	1.49921	1.51307	1.52508	1.53528	1.54352	-30.50	-24.96	-19.21	-14.02	-8.48
0.1215	1.50749	1.52108	1.53286	1.54278	1.55070	-29.66	-24.01	-18.60	-13.40	-7.85
	0.010 mol·kg <sup>-1</sup> $[C_4mim][Cl]$ + DPH									
0.0000	1.48350	1.49769	1.51022	1.52092	1.52971					
0.0015	1.48381	1.49799	1.51047	1.52120	1.52998	-30.99	-25.35	-19.40	-13.99	-8.22
0.0045	1.48443	1.49859	1.51105	1.52176	1.53052	-30.96	-25.32	-19.36	-13.95	-8.16
0.0135	1.48628	1.50039	1.51279	1.52344	1.53212	-30.81	-25.18	-19.28	-13.79	-8.02
0.0405	1.49184	1.50580	1.51801	1.52846	1.53693	-30.45	-24.87	-18.99	-13.40	-7.62
0.0805	1.50005	1.51377	1.52572	1.53587	1.54400	-29.98	-24.34	-18.59	-12.94	-7.08
0.1215	1.50845	1.52191	1.53359	1.54342	1.55119	-29.55	-23.83	-18.15	-12.45	-6.52
	0.020 mol·kg <sup>-1</sup> $[C_4mim][Cl]$ + DPH									
0.0000	1.48464	1.49878	1.51125	1.52183	1.53056					
0.0015	1.48495	1.49908	1.51154	1.52211	1.53083	-29.99	-23.52	-17.87	-13.08	-7.16
0.0045	1.48557	1.49968	1.51212	1.52267	1.53136	-29.95	-23.47	-17.84	-13.03	-7.09
0.0135	1.48743	1.50147	1.51386	1.52435	1.53298	-29.82	-23.36	-17.74	-12.87	-6.93
0.0405	1.49300	1.50685	1.51906	1.52939	1.53779	-29.38	-22.92	-17.38	-12.40	-6.58
0.0805	1.50121	1.51477	1.52673	1.53681	1.54487	-28.78	-22.33	-16.84	-11.88	-6.05
0.1215	1.50959	1.52285	1.53454	1.54435	1.55206	-28.17	-21.77	-16.26	-11.28	-5.45
	0.040 mol·kg <sup>-1</sup> $[C_4mim][Cl]$ + DPH									
0.0000	1.48816	1.50195	1.51416	1.52461	1.53323					
0.0015	1.48847	1.50225	1.51445	1.52489	1.53350	-28.68	-22.52	-17.14	-11.68	-5.72
0.0045	1.48909	1.50285	1.51503	1.52545	1.53403	-28.57	-22.45	-17.09	-11.61	-5.64
0.0135	1.49095	1.50465	1.51678	1.52713	1.53564	-28.39	-22.30	-16.94	-11.49	-5.48
0.0405	1.49653	1.51005	1.52202	1.53218	1.54045	-27.87	-21.82	-16.65	-11.12	-5.05
0.0805	1.50473	1.51800	1.52975	1.53961	1.54753	-27.09	-21.20	-16.26	-10.61	-4.61
0.1215	1.51308	1.52609	1.53761	1.54717	1.55475	-26.33	-20.53	-15.66	-10.05	-4.11
	0.005 mol·kg <sup>-1</sup> $[C_6mim][Cl]$ + DPH									
0.0000	1.48291	1.49745	1.50975	1.52042	1.52969					
0.0015	1.48309	1.49770	1.50999	1.52055	1.52973	-31.26	-25.63	-19.72	-13.62	-8.02
0.0045	1.48371	1.49831	1.51057	1.52111	1.53027	-31.21	-25.57	-19.62	-13.57	-7.97
0.0135	1.48558	1.50012	1.51233	1.52279	1.53188	-31.09	-25.35	-19.50	-13.42	-7.79
0.0405	1.49118	1.50556	1.51759	1.52783	1.53672	-30.73	-24.96	-19.19	-13.00	-7.52
0.0805	1.49945	1.51358	1.52537	1.53525	1.54384	-30.20	-24.40	-18.81	-12.49	-7.04
0.1215	1.50791	1.52177	1.53328	1.54279	1.55106	-29.72	-23.81	-18.21	-11.87	-6.45
	0.010 mol·kg <sup>-1</sup> $[C_6mim][Cl]$ + DPH									
0.0000	1.48389	1.49765	1.51043	1.52108	1.53034					
0.0015	1.48414	1.49786	1.51061	1.52118	1.53065	-29.14	-23.61	-18.07	-12.38	-6.88
0.0045	1.48476	1.49846	1.51119	1.52174	1.53119	-29.09	-23.55	-18.02	-12.33	-6.81
0.0135	1.48661	1.50027	1.51294	1.52342	1.53280	-28.92	-23.42	-17.86	-12.18	-6.67
0.0405	1.49215	1.50567	1.51817	1.52846	1.53764	-28.20	-22.98	-17.37	-11.77	-6.33
0.0805	1.50032	1.51365	1.52588	1.53588	1.54476	-27.59	-22.49	-16.84	-11.25	-5.83
0.1215	1.50863	1.52178	1.53374	1.54344	1.55200	-26.83	-21.84	-16.21	-10.64	-5.24
	0.020 mol·kg <sup>-1</sup> $[C_6mim][Cl]$ + DPH									

Table 4. continued

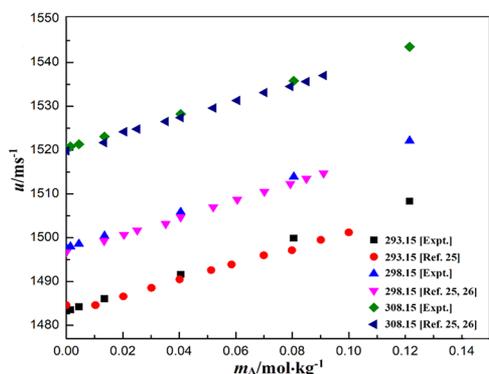
$^a m_A$ (mol·kg <sup>-1</sup> )	$u \times 10^3$ (m·s <sup>-1</sup> )					$K_\phi \times 10^{15}$ (m <sup>3</sup> ·mol <sup>-1</sup> ·Pa <sup>-1</sup> )				
	temp.					temp.				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	1.48584	1.49961	1.51197	1.52253	1.53124					
0.0015	1.48608	1.49982	1.51214	1.52265	1.53137	-27.38	-21.67	-16.33	-11.26	-5.68
0.0045	1.48670	1.50042	1.51272	1.52321	1.53191	-27.26	-21.62	-16.29	-11.20	-5.59
0.0135	1.48855	1.50222	1.51446	1.52490	1.53352	-27.11	-21.46	-16.13	-11.03	-5.23
0.0405	1.49410	1.50760	1.51968	1.52994	1.53833	-26.84	-21.11	-15.74	-10.64	-4.69
0.0805	1.50230	1.51555	1.52738	1.53737	1.54541	-26.36	-20.63	-15.26	-10.12	-4.13
0.1215	1.51067	1.52365	1.53522	1.54492	1.55262	-25.81	-20.04	-14.64	-9.45	-3.56
						0.040 mol·kg <sup>-1</sup> [C <sub>6</sub> mim][Cl] + DPH				
0.0000	1.49005	1.50358	1.5157	1.52592	1.53507					
0.0015	1.49025	1.50373	1.51581	1.52597	1.53528	-26.42	-20.45	-15.39	-9.90	-4.40
0.0045	1.49087	1.50433	1.51639	1.52653	1.53582	-26.37	-20.39	-15.34	-9.85	-4.35
0.0135	1.49273	1.50613	1.51815	1.52822	1.53744	-26.22	-20.18	-15.20	-9.67	-4.22
0.0405	1.49832	1.51152	1.52339	1.53327	1.54228	-25.86	-19.62	-14.79	-9.33	-3.83
0.0805	1.50657	1.51948	1.53112	1.54071	1.54940	-25.35	-19.15	-14.26	-8.85	-3.32
0.1215	1.51499	1.52761	1.53899	1.54825	1.55663	-24.75	-18.61	-13.64	-8.11	-2.71
						0.005 mol·kg <sup>-1</sup> [C <sub>8</sub> mim][Cl] + DPH				
0.0000	1.48407	1.49841	1.51102	1.52111	1.52997					
0.0015	1.48438	1.49871	1.51131	1.52139	1.53024	-29.99	-24.51	-18.70	-13.07	-7.55
0.0045	1.48501	1.49932	1.51190	1.52196	1.53079	-29.90	-24.45	-18.66	-12.98	-7.50
0.0135	1.48688	1.50115	1.51367	1.52366	1.53242	-29.72	-24.33	-18.55	-12.83	-7.36
0.0405	1.49250	1.50663	1.51897	1.52876	1.53732	-29.18	-23.94	-18.16	-12.46	-7.03
0.0805	1.50080	1.51472	1.52681	1.53628	1.54455	-28.60	-23.39	-17.70	-11.93	-6.60
0.1215	1.50927	1.52299	1.53481	1.54392	1.55189	-27.98	-22.86	-17.14	-11.29	-5.98
						0.010 mol·kg <sup>-1</sup> [C <sub>8</sub> mim][Cl] + DPH				
0.0000	1.48497	1.49901	1.51156	1.52191	1.53077					
0.0015	1.48528	1.49923	1.51174	1.52196	1.53150	-27.80	-22.21	-16.80	-11.01	-5.60
0.0045	1.48590	1.49983	1.51232	1.52252	1.53204	-27.74	-22.13	-16.75	-10.95	-5.55
0.0135	1.48776	1.50165	1.51408	1.52421	1.53366	-27.6	-21.97	-16.60	-10.79	-5.41
0.0405	1.49335	1.50708	1.51935	1.52927	1.53853	-27.21	-21.57	-16.21	-10.38	-5.09
0.0805	1.50161	1.51511	1.52713	1.53673	1.54571	-26.73	-21.13	-15.77	-9.89	-4.71
0.1215	1.51004	1.52330	1.53505	1.54432	1.55302	-26.13	-20.53	-15.17	-9.31	-4.18
						0.020 mol·kg <sup>-1</sup> [C <sub>8</sub> mim][Cl] + DPH				
0.0000	1.48723	1.50128	1.51346	1.52382	1.53256					
0.0015	1.48754	1.50150	1.51359	1.52396	1.53239	-26.11	-20.32	-14.58	-8.92	-3.39
0.0045	1.48816	1.50210	1.51417	1.52452	1.53292	-26.05	-20.25	-14.52	-8.87	-3.34
0.0135	1.49002	1.50391	1.51592	1.52620	1.53453	-25.92	-20.13	-14.36	-8.73	-3.18
0.0405	1.49560	1.50932	1.52114	1.53122	1.53935	-25.48	-19.72	-13.98	-8.32	-2.84
0.0805	1.50383	1.51731	1.52885	1.53862	1.54645	-24.90	-19.25	-13.52	-7.83	-2.44
0.1215	1.51222	1.52546	1.53669	1.54614	1.55368	-24.25	-18.72	-12.92	-7.22	-1.95
						0.040 mol·kg <sup>-1</sup> [C <sub>8</sub> mim][Cl] + DPH				
0.0000	1.49286	1.50667	1.51847	1.52838	1.53692					
0.0015	1.49302	1.50674	1.51845	1.52823	1.53657	-24.41	-18.94	-13.48	-7.60	-1.86
0.0045	1.49364	1.50734	1.51903	1.52879	1.53710	-24.36	-18.81	-13.44	-7.42	-1.81
0.0135	1.49550	1.50915	1.52079	1.53047	1.53871	-24.24	-18.67	-13.34	-7.38	-1.69
0.0405	1.50110	1.51457	1.52604	1.53549	1.54353	-23.91	-18.15	-12.94	-6.83	-1.40
0.0805	1.50936	1.52259	1.53378	1.54291	1.55062	-23.46	-17.87	-12.45	-6.53	-0.97
0.1215	1.51778	1.53077	1.54167	1.55044	1.55782	-22.85	-17.40	-11.94	-5.95	-0.39

<sup>a</sup> $m_A$  represents the molality of DPH in aqueous IL solution. Standard uncertainties are  $u(p) = 0.01$  MPa,  $u(T) = 0.01$  K,  $u(u) = 2 \text{ m} \cdot \text{s}^{-1}$ ,  $u(m) = 2 \times 10^{-3} \text{ mol} \cdot \text{kg}^{-1}$ , and  $u(K_\phi) = (0.04-0.07) \times 10^{15} \text{ m}^3 \cdot \text{mol}^{-1} \cdot \text{Pa}^{-1}$ .

correspond to ionic compounds; and negative, small, and intermediate values correspond to uncharged hydrophilic solutes.<sup>54-56</sup> Figures 5-7 represent the plots of apparent molar isentropic compressibility ( $K_\phi$ ) versus molality ( $m_A$ ) of DPH in aqueous solutions of [C<sub>4</sub>mim][Cl], [C<sub>6</sub>mim][Cl], and [C<sub>8</sub>mim][Cl] at different temperatures.

With increase in temperature,  $K_\phi$  values become less negative. The negative  $K_\phi$  values signify that water molecules are more

compressible in the bulk solution as compared to water molecules surrounding the ionic charged groups of ILs, which clearly indicates strong solute-solvent interaction between the ions of ILs and DPH molecules.<sup>30,56</sup> In other words, the negative  $K_\phi$  values indicate greater loss of structural compressibility of water, implying a greater ordering effect by the solute on the solvent. However, with increase in the concentration of the DPH or concentration of ILs, a large portion of the water molecule



**Figure 5.** Comparison of experimental and literature values<sup>25,26</sup> of speed of sound of DPH + water mixture at three different temperatures.

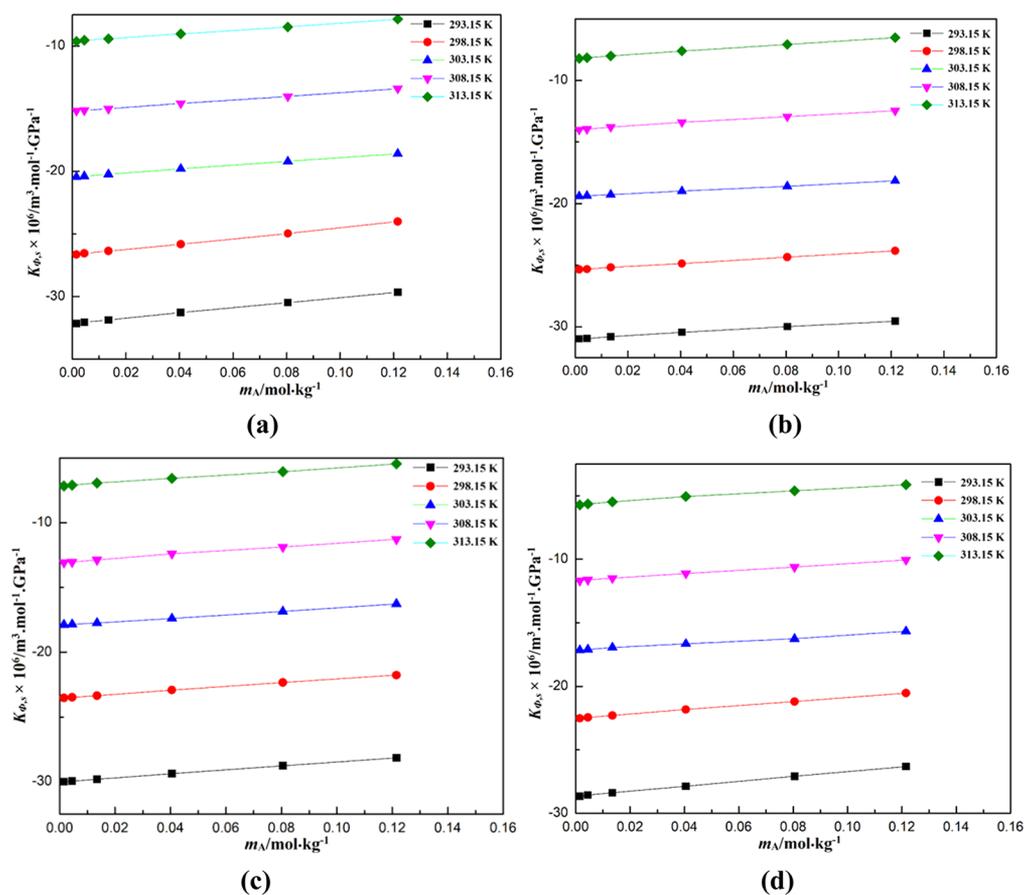
gets electrostricted, which ultimately decreases the amount of bulk water, causing decline in the compressibility, which can be further attributed to the strong attractive interactions. The negative values of  $K_\phi$  demonstrate the preponderance of hydrophilic–ionic interactions,<sup>33</sup> which is further supported by our  $V_\phi$  data as seen in Figure 8.

### 2.2.2. Apparent Partial Molar Isentropic Compressibility.

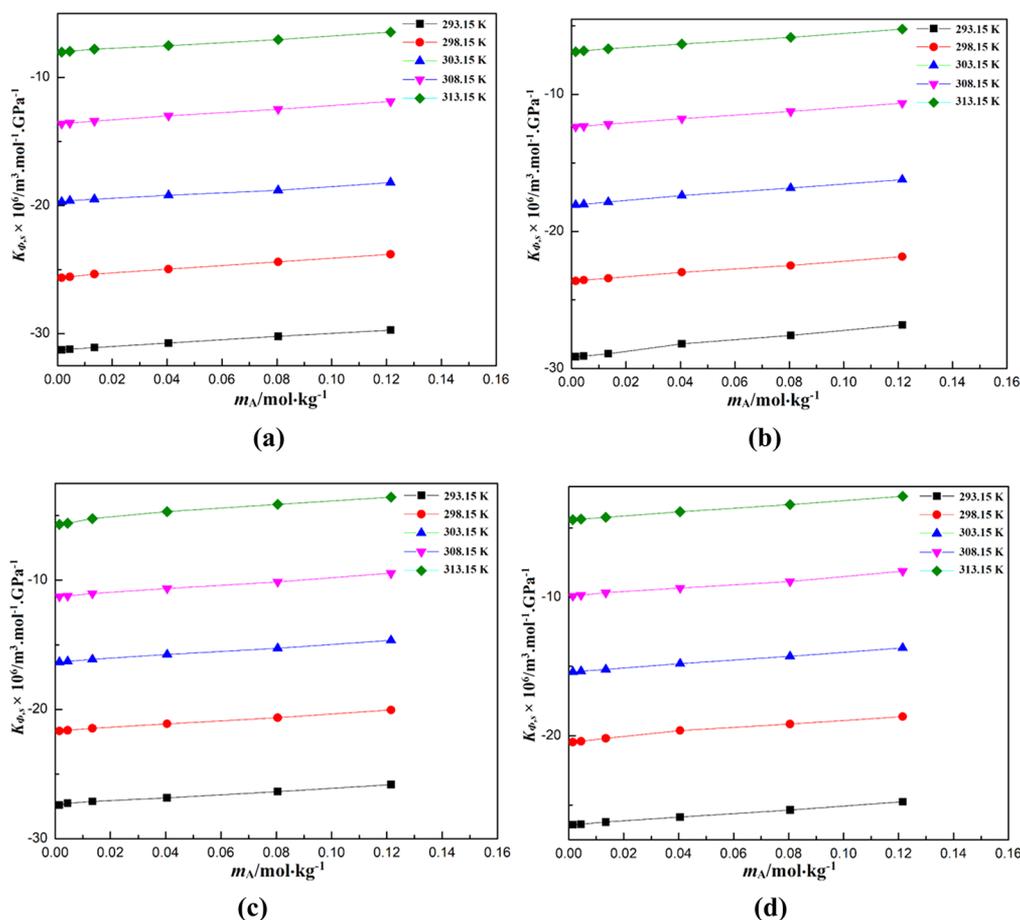
The variation of the apparent molar isentropic compressibility ( $K_\phi$ ) with the molal concentration can be represented by following equations<sup>19,30</sup>

$$K_\phi = K_\phi^o + S_K^* m_A \quad (15)$$

where  $K_\phi^o$  is the limiting value of the isentropic compressibility and  $S_K^*$  is the experimental slope indicative of DPH–DPH interactions. The values of  $K_\phi^o$  and  $S_K^*$  are obtained from the extrapolation of the apparent molar compressibility  $K_\phi$  at an infinite dilution using eq 15 and are reported in Table S6. The drug under consideration has negative  $K_\phi^o$  values in aqueous IL solutions at different temperatures, thereby reflecting the presence of strong solute–solute interactions.<sup>19,30</sup> However, as we move to higher temperatures, the  $K_\phi^o$  values become less and less negative, which indicates simultaneous reduction of electrostriction and release of some water molecules to the bulk of the solution. The strong attractive interactions owing to hydration of ions generated from the dissociation of ILs results in the dehydration of DPH and corresponding increase in the number of water molecules in the bulk. Therefore, at high IL concentrations, the water molecules around the DPH are more compressible than those at lower concentrations of ILs. However, with the increase in the alkyl chain length of the ILs, we obtain lesser negative values, which suggests the prevalence of stronger solute–solvent interaction in case of  $[C_8\text{mim}][\text{Cl}]$  compared with  $[C_6\text{mim}][\text{Cl}]$  and  $[C_4\text{mim}][\text{Cl}]$ .<sup>30</sup> Hence, the overall solute–solvent interaction follows the order  $[C_8\text{mim}][\text{Cl}] > [C_6\text{mim}][\text{Cl}] > [C_4\text{mim}][\text{Cl}]$ . The positive but lesser values of the slope  $S_K^*$  signify the presence of weak solute–solute interactions in the system. The values of  $S_K^*$  decrease as we move to higher temperatures, whereas the values increase with increase in drug concentration for all ILs.



**Figure 6.** Plots of apparent molar isentropic compressibility ( $K_\phi$ ) versus molality ( $m_A$ ) of (a) DPH in 0.005 mol·kg<sup>-1</sup>, (b) DPH in 0.010 mol·kg<sup>-1</sup>, (c) DPH in 0.020 mol·kg<sup>-1</sup>, and (d) DPH in 0.040 mol·kg<sup>-1</sup> aqueous  $[C_4\text{mim}][\text{Cl}]$  solution at different temperatures.

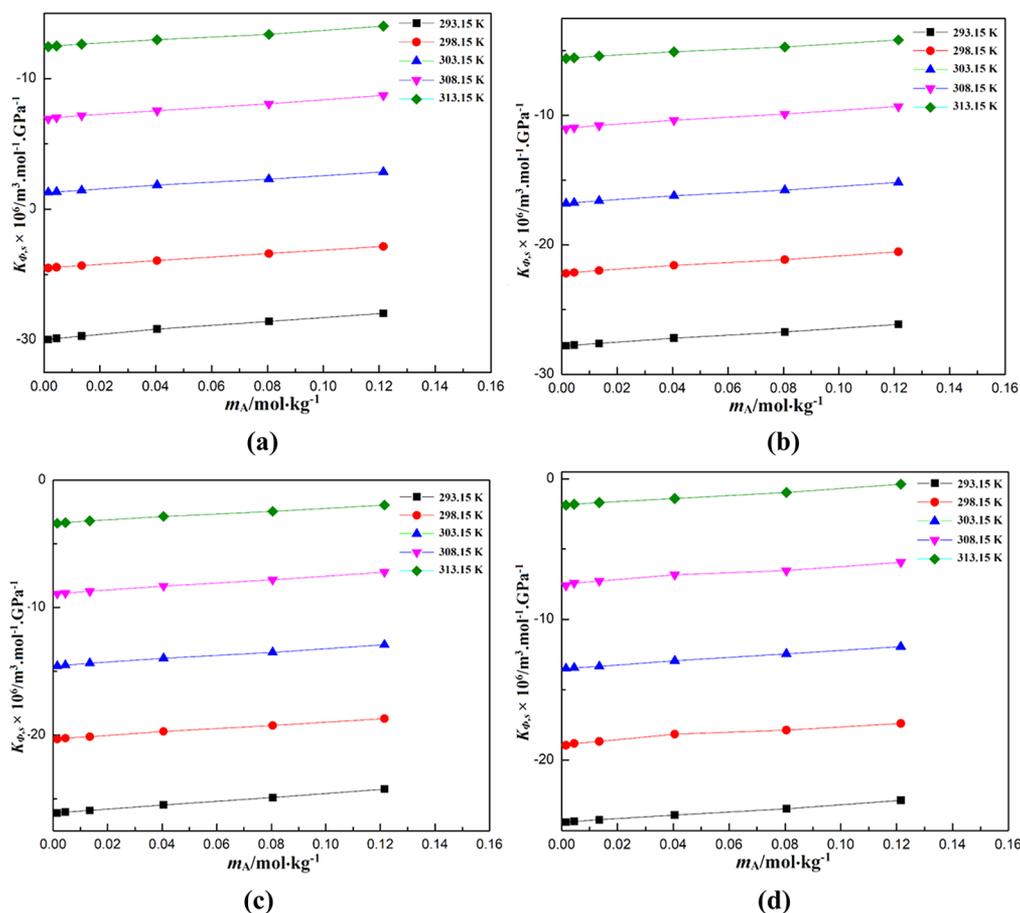


**Figure 7.** Plots of apparent molar isentropic compressibility ( $K_\phi$ ) versus molality ( $m_A$ ) of (a) DPH in  $0.005 \text{ mol}\cdot\text{kg}^{-1}$ , (b) DPH in  $0.010 \text{ mol}\cdot\text{kg}^{-1}$ , (c) DPH in  $0.020 \text{ mol}\cdot\text{kg}^{-1}$ , and (d) DPH in  $0.040 \text{ mol}\cdot\text{kg}^{-1}$  aqueous  $[\text{C}_6\text{mim}][\text{Cl}]$  solution at different temperatures.

The partial molar isentropic compressibility of transfer ( $\Delta_t K_\phi^\circ$ ) is calculated using eq E1 of the Supporting Information, and the obtained values are reported in Table S7 of the Supporting Information. The  $\Delta_t K_\phi^\circ$  values are positive for DPH in aqueous solutions of ILs and indicate the dominant interactions occurring between the ions of the drug and the ionic liquid, resulting in the enhanced structure-making tendency of the ions.<sup>38</sup> There occurs increased interactions between the ions of the drug and ionic liquids with an increase in IL concentration. The increase in the IL concentrations results in decreased electrostriction, consequently increasing the structure-making tendency of the ions. As a result, the electrostricted water becomes much less compressible than the bulk water, resulting in an abrupt decrease in the compressibility with an increase in IL concentration. Consequently,  $K_\phi^\circ$  values are negative, whereas  $\Delta_t K_\phi^\circ$  values become positive for drugs in aqueous solutions of ILs. This may be due to the reason that an extra water molecule is associated with the ion at a lower temperature as well as at lower concentrations of ILs; the larger the number of water molecules of solute associated with the solvent molecules, the more the solute–solvent interaction.<sup>30</sup> However, with increase in the alkyl chain length of ionic liquids, the value of  $\Delta_t K_\phi^\circ$  becomes more positive, which is a clear indication of the stronger solute–solvent interaction in the system. Therefore, the order will be  $[\text{C}_8\text{mim}][\text{Cl}] > [\text{C}_6\text{mim}][\text{Cl}] > [\text{C}_4\text{mim}][\text{Cl}]$ .

### 3. ABSORPTION SPECTRAL STUDIES

To unravel the solute–solute interactions for the ternary systems, the UV–visible absorption spectra of different mixtures were analyzed. The absorption spectra of DPH with molality 0.05, 0.10, 0.15, and 0.20 mM in aqueous solutions of  $[\text{C}_4\text{mim}][\text{Cl}]$ ,  $[\text{C}_6\text{mim}][\text{Cl}]$ , and  $[\text{C}_8\text{mim}][\text{Cl}]$  with different molarities (0.10 and 0.50 mM) are given in Figure 9. The intense signal around 220–210 nm in the absorption spectra can be ascribed to the  $\pi-\pi^*$  transitions that originate from the  $\text{C}=\text{C}$  bond of imidazolium ion moiety.<sup>57</sup> From the absorption spectra, it can be inferred that the intensity of absorption maximum increases with increasing DPH concentration for a fixed molality of ionic liquid. Also, there is a slight shift toward a lower wavelength with increase in the concentration of DPH. If we increase the concentration of the same ionic liquid, the intensity of the absorption maximum increases as compared to a lower molality of ionic liquid; on adding DPH with the same concentration as previously, there is again a slight shift toward a lower wavelength. The recorded absorption spectra seem to be affected by varying the alkyl chain length of the ionic liquids. In particular, in the investigated range, all three ionic liquids ( $[\text{C}_4\text{mim}][\text{Cl}]$ ,  $[\text{C}_6\text{mim}][\text{Cl}]$ , and  $[\text{C}_8\text{mim}][\text{Cl}]$ ) exhibit intense absorption; however, a decrease in absorbance has been detected on increasing the alkyl chain length. This can be due to the formation of reasonably different associated structures, whose extent could be limited in the presence of longer alkyl chains.<sup>58</sup> Furthermore, the absorption spectra of all three ILs showed a regular trend with a slight hypsochromic shift



**Figure 8.** Plots of apparent molar isentropic compressibility ( $K_\phi$ ) versus molality ( $m_A$ ) of (a) DPH in  $0.005 \text{ mol}\cdot\text{kg}^{-1}$ , (b) DPH in  $0.010 \text{ mol}\cdot\text{kg}^{-1}$ , (c) DPH in  $0.020 \text{ mol}\cdot\text{kg}^{-1}$ , and (d) DPH in  $0.040 \text{ mol}\cdot\text{kg}^{-1}$  aqueous  $[\text{C}_8\text{mim}][\text{Cl}]$  solution at different temperatures.

with corresponding increase in DPH molarity from 0.05 mM to 0.20 mM, thereby supporting our experimental data. This trend is in appreciable accordance with the volumetric and acoustic results. The shift observed in the case of  $(\text{IL}_1) = [\text{C}_4\text{mim}][\text{Cl}]$ ,  $(\text{IL}_2) = [\text{C}_6\text{mim}][\text{Cl}]$ , and  $(\text{IL}_3) = [\text{C}_8\text{mim}][\text{Cl}]$ .

Our study involving DPH with ILs indicates the coordination of the ions of DPH with ionic liquids by breaking the solvent layer of water, which causes extended conjugation resonance as clearly supported by our thermodynamic data.<sup>59</sup>

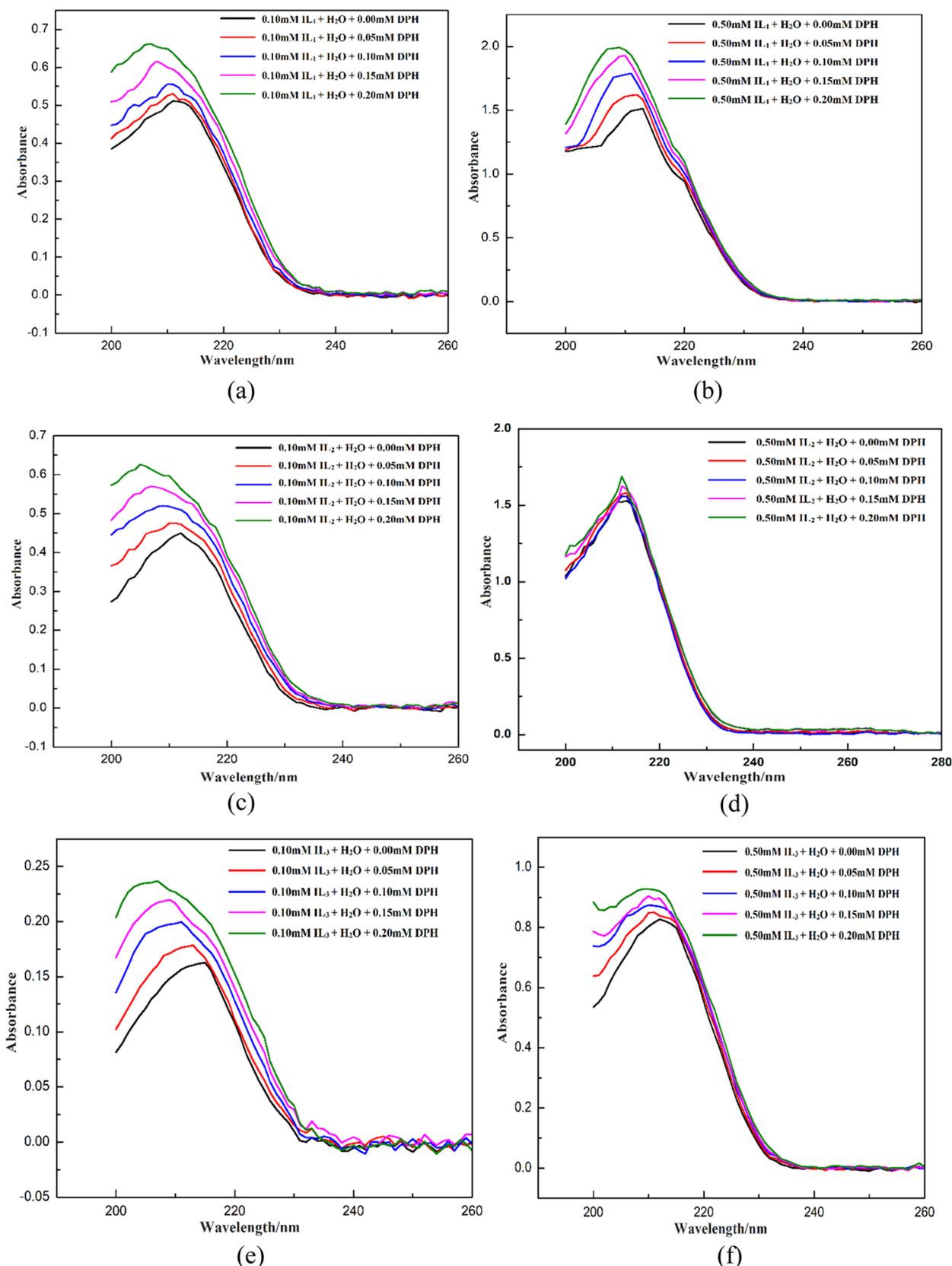
#### 4. CONCLUSIONS

In the present work, we attempt to study the interaction between the DPH drug and three imidazolium ionic liquids in aqueous medium via a volumetric and acoustic approach. The apparent partial molar volume ( $V_\phi$ ) and the partial molar isentropic compressibility ( $K_\phi$ ) were evaluated from experimental density and acoustic data, respectively. It was found that both these quantities showed an enhanced trend with increasing ionic liquid concentration in all of the ternary systems. Moreover, the interactions between DPH and the ionic liquids were strengthened with increasing ionic liquid concentrations. Also, these interactions increase with the increase in size of the alkyl chain length of the ionic liquids. There occur strong solute–solvent interactions in the ternary system, which is confirmed by the derived partial molar properties of transfer. The Helper's constant  $(\partial E_\phi^\circ / \partial T)_P$  calculation finally concludes DPH as a structure maker, and its structure-making behavior increases with increasing ionic liquid concentrations. From the UV data, a

general increase in the intensity of the absorption maxima with the increase in ionic liquid concentrations and with the addition of a small amount of DPH is observed. Further, a hypsochromic shift is observed with the addition of a small amount of DPH in aqueous ionic liquid solution, which indicates that the solute–solvent interaction is prevailing in the ternary system. Finally, the present results confirm the presence of strong ionic–hydrophilic and hydrophilic–hydrophilic interactions between the DPH molecules and the ionic liquids, and the comprehensive behavior of these interactions in getting more stronger with the increase in size of the alkyl chain length of the ionic liquids.

#### EXPERIMENTAL SECTION

**Chemicals.**  $[\text{C}_4\text{mim}][\text{Cl}]$  and  $[\text{C}_8\text{mim}][\text{Cl}]$  were purchased from Tokyo Chemicals Industry Co. Ltd., India, with a mass fraction purity  $\geq 0.985$ . DPH with a mass fraction purity  $> 0.99$  was also obtained from Tokyo Chemicals Industry Co. Ltd., India. Similarly,  $[\text{C}_6\text{mim}][\text{Cl}]$  with a mass fraction purity  $\geq 0.98$  was purchased from Thermo Fisher Scientific, India. The three ILs were dried under high vacuum at 343.15 K overnight to remove any moisture content. The water content was checked using Karl Fischer analysis, which records values less than 350 ppm. Further, before their actual use in the present study, the chemicals were dried properly and stored in vacuum desiccators over  $\text{P}_2\text{O}_5$  for about 2 days. The specifications of the chemicals under investigation and their respective structures are provided in Table S1 of the Supporting Information.



**Figure 9.** Absorption spectra of aqueous solutions of ionic liquids (a) 0.10 mM IL<sub>1</sub>, (b) 0.50 mM IL<sub>1</sub>, (c) 0.10 mM IL<sub>2</sub>, (d) 0.50 mM IL<sub>2</sub>, (e) 0.10 mM IL<sub>3</sub>, and (f) 0.50 mM IL<sub>3</sub> with different molarities (0.05, 0.10, 0.15, and 0.20 mM) of DPH.

**Apparatus and Procedures.** The binary (DPH + water) and ternary (DPH + water + ILs) solutions were prepared by weighing on a single-pan four-digit analytical balance (Mettler

Toledo, Model: ML204) having a standard uncertainty of 0.00001 g. Freshly prepared triple and de-ionized water with a specific conductance less than  $10^{-6}$  was used for the preparation

of the solutions. The prepared solutions were then sealed in airtight flasks to check their moisture captivation from the surrounding atmosphere. The densities  $\rho$  and speeds of sound  $u$  were measured using an Anton Paar DSA5000 M densimeter at a low frequency (approximately 3 MHz). The densimeter was initially calibrated with triply distilled de-ionized/degassed water and dry air at atmospheric pressure in each series of measurements. Due to the high sensitivities of density and speed of sound to temperature, to control the temperature within the densimeter to  $\pm 1.0 \times 10^{-3}$  K, a built-in Peltier thermostat was utilized. A density check or an air/water adjustment was performed at 293.15 K with triply distilled water in the experimental range 293.15–313.15 K. The standard uncertainty of density and speed-of-sound measurements was found to be within  $0.001 \text{ kg}\cdot\text{m}^{-3}$  and  $0.01 \text{ m}\cdot\text{s}^{-1}$ , respectively. UV–visible spectra were recorded using a PG spectrophotometer, model T-90. The spectral range of the instrument is 200–800 nm. The UV–visible absorption spectra were recorded for the mixtures to analyze the presence of solute–solvent interactions within the spectral range of 200–350 nm at room temperature.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c02733>.

Representative plot of Apparent partial molar volumes of transfer ( $\Delta_t V_\phi^\circ$ ), representative plot of apparent partial molar isentropic compressibility of transfer ( $\Delta_t K_\phi^\circ$ ), table of specification of chemicals, tables containing data of limiting apparent molar volumes ( $V_\phi^\circ$ ) and experimental slopes ( $S_V^*$ ), Apparent partial molar volumes of transfer ( $\Delta_t V_\phi^\circ$ ), values of empirical parameters ( $A$ ,  $B$ , and  $C$ ), hydration number ( $n_H$ ), Limiting apparent molar adiabatic compressibility ( $K_\phi^\circ$ ) and experimental slopes ( $S_K^*$ ) and apparent partial molar isentropic compressibility of transfer ( $\Delta_t K_\phi^\circ$ ) (PDF)

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<https://pubs.acs.org/doi/10.1021/acsomega.1c02733>

### Notes

The authors declare no competing financial interest.

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